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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/464,795	ZHANG ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38,40,41,43,45,46,49,65-68 and 80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38,40,41,43,45,46,49,65-68 and 80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 December 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/27/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed February 18, 2005 (herein after referred to as "the response") has been entered. Claims 38 and 65 have been amended. Claim 80 has been newly added.

Accordingly, Claims 38, 40, 41, 43, 45, 46, 49, 65-68, and 80 are pending in the instant application.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Product of Nature

Claim 80 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claim 80 is directed to an ancestor of the transgenic mouse of Claim 38.

The claim reads on a wild-type mouse, which is a product of nature and is therefore non-statutory subject matter.

Utility

Claims 38, 40, 41, 43, 45, 46, 49, and 65-68 stand rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

A careful reading of the specification indicates only one asserted utility for transgenic mice comprising multiple expression cassettes as recited in the claims. The asserted utility is to use the mice to identify agents that induce expression of the reporter gene (i.e., the "light generating polypeptide") with the express purpose of determining how various agents present in the environment affect native gene

expression in humans and other animals and, more specifically, how the agents affect the particular control elements present in the reporter constructs. However, the instant claims cover a great variety of transgenic mice that cannot be used for the asserted utility because they would not be useful in assaying agents to determine how they affect native gene expression. For example, the claims cover a wide variety of transgenic mice that have control elements and combinations of control elements that are in no way representative of the native expression of the genes from which they are derived. Thus, the skilled artisan would not be able to correlate the result obtained by carrying out a screening assay as defined, for example, in Claim 40, to the function of the pertinent control elements in their native context.

With regard to the control element recited in the claims, the specification discloses the following at page 33:

"The control element (e.g., a promoter) may be from the same species as the transgenic animal (e.g., mouse promoter used in construct to make transgenic mouse), from a different species (e.g., human promoter used in construct to make transgenic mouse), or a mixed control element (e.g., some control elements from a mouse promoter combined with some control elements of a human promoter)." Specification at page 33, lines 26-30.

The specification further discloses, at pages 11-12, that the "control element derived from a ... stress-inducible gene" may be as follows:

"Typical control elements or expression control elements or regulatory sequences, include, but are not limited to transcription promoters, transcription enhancer elements, transcription termination signals, polyadenylation sequences (located 3' to the translation stop codon), sequences for optimization of initiation of translation (located 5' to the coding sequence), translation enhancing sequences, and translation termination sequences. Transcription promoters can include inducible promoters (where expression of a polynucleotide sequence operably linked to the promoter is induced by an analyte, cofactor, regulatory protein, etc.), repressible promoters (where expression of a polynucleotide sequence operably linked to the promoter is induced by an analyte, cofactor, regulatory protein, etc.), and constitutive promoters.

Expression enhancing sequences typically refer to control elements that improve transcription or translation of a polynucleotide relative to the expression level in the absence of such control elements (for

example, promoters, promoter enhancers, enhancer elements, and translational enhancers (e.g., Shine and Delagarno [sic] sequences))." Specification at pages 11-12.

At page 6 of the response, Applicants assert that the Examiner's statements in the prior Office Action indicate that the Examiner believes that Applicants' utility is credible since credibility has not been challenged. Applicants are incorrect in leaping to this conclusion because credibility is not assessed and clearly cannot be assessed when a specific and substantial utility is lacking. The asserted utility, as discussed above, is not applicable to the vast majority of animals covered by the claims. Thus, an asserted utility is lacking for a very large scope of the claims.

At page 6 of the response, Applicants assert that they have provided both a specific and substantial asserted utility **and** a well-established utility. Applicants go on to argue that the transgenic mice of the invention can be used to determine an analyte's effect on the "two or more stress-inducible control elements in the mice." First and foremost, it is noted that the claims do not require the presence of a single "stress-inducible control element" in the mice. On the contrary, the claims recite the use of a "control element derived from a ... stress-inducible gene." Thus, the particular control element included in the expression cassette need not be a **stress-inducible** control element. Therefore, Applicants are arguing limitations not in the claims. Second, even if the claims did recite the presence of a stress-inducible control element, the context in which the control element resides (e.g., combined with other unrelated control elements and/or inserted into the genome within a site that is influenced by the endogenous control elements surrounding the expression cassettes) is in no way required to correlate with the native context of the genetic control elements. In such cases, the function of the artificial construct would in no way pertain to the function of the control elements in their native context.

At page 7, paragraph 2 of the response, Applicants assert that Jankowsky et al. (2001) confirms the asserted utility. Contrary, to Applicants assertion Jankowsky does not pertain to the instant grounds of rejection and further cannot confirm the asserted utility because its teachings do not pertain to the instantly claimed invention. However, the instant claims cover a great variety of transgenic mice,

harboring a great variety of transgene constructs that are unrelated to the disclosure of Jankowsky. Applicants' arguments are not commensurate in scope with the scope of the claims. The claims cover the use of constructs that have no bearing on native gene expression. The MPEP advises that "[i]n such cases, the applicant should be encouraged to amend the generic claim so as to exclude the species that lack utility" (MPEP 2107.02(I)). However, in the instant case, the Examiner finds no language within the specification that points specifically to the genus of constructs that would produce transgenic mice **useful for the asserted utility**, which is to provide an assay system to determine the effect of various agents on the control elements in a manner that correlates to the native function of the element in its native context. The specification provides no assertion of utility whatsoever for artificial constructs that have no bearing on native gene function.

At page 7, paragraph 2 of the response, Applicants assert that "**when the two or more stress-inducible promoters are induced,** the claimed mice would produce luciferase at high levels." Again, Applicants are arguing limitations that are not in the claims because the **claimed** invention does not require the presence of a "stress-inducible promoter." The mere presence of a polyadenylation signal "derived from a first stress-inducible gene" and another identical polyadenylation signal "derived from a second stress-inducible gene" would be sufficient to meet the claim limitations (Claim 38) and would be induced by **nothing**. See the specification at page 11, lines 24-26 which states that "[t]ypical control elements ... include ... polyadenylation sequences." The promoter can be any promoter at all. There is nothing in the claim that limits the promoter (or even requires a promoter). Applicants arguments are far afield from that which is claimed. Clearly, there is **no** specific and substantial utility for transgenic mice bearing such constructs, because **the asserted utility does not pertain to such mice.**

At page 7, paragraph 3 of the response, Applicants assert that they have provided "a well-established utility, for the molecules of the present invention." Since the claims are not directed to "molecules" it will be assumed that Applicants are referring to the transgenic mice. However, no support

is provided for the assertion that Applicants have provided a well-established utility. If Applicants now wish to rely on a **well-established** utility, they must actually identify what the well-established utility is. There is no mention of any specific well-established utility.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 38, 40, 41, 43, 45, 46, 49, and 65-68 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advance in the prior Office Actions of 2/1/01, 9/13/01, 8/27/02, 5/21/03, 10/5/04, and as further discussed herein, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

At page 7, paragraph 6 of the response, Applicants assert that the description in the specification of the method of producing the transgenic mouse and product-by-process claim language is sufficient to obviate the rejection. On the contrary, a method of making is not sufficient to describe the very broadly claimed transgenic mouse. The claims recite mice comprising transgene constructs that comprise a wide variety of control elements. The control elements are an essential element of the claimed invention and neither the specification nor the prior art sufficiently describes the full array of control elements covered by the claims. The skilled artisan would be required to rely on the teachings of the prior art for extensive teachings relating to the full array of native control elements of any gene that falls within the scope of the

claim. However, the prior art does not provide a description of the necessary native control elements for the very large genus of stress-inducible genes covered by the claims.

Thus, the rejection is maintained for reasons of record.

Enablement

Claims 38, 40, 41, 43, 45, 46, 49, and 65-68 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advance in the prior Office Actions of 2/1/01, 9/13/01, 8/27/02, 5/21/03, 10/5/04, and as further discussed herein, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

At page 8 of the response, Applicants assert that making transgenic mice with multiple expression cassettes is predictable and routine because transgenic mice expressing light generating proteins have been made. However, the existence of transgenic mice expressing light generating proteins is not sufficient to enable the claimed invention because the **claimed** invention requires the generation of transgenic mice having inducible control elements that regulate expression of the light generating proteins in a manner that is predictive of native gene expression (the only asserted utility for the claimed transgenic mouse). The particular control elements used and the method of inserting the expression cassettes into the genome of the mouse are critical to the operability of the claimed invention.

Applicants further assert that the skilled artisan "would instantaneously know from the specification that the claimed transgenic animals would be characterized by light-generation when administered an analyte that induces one or more of the transgenic stress-inducible control sequences." First and foremost, it is noted that the claims are not directed to and do not require the presence of a "stress-inducible control sequences." On the contrary, the claims recite the use of a "control element derived from a ... stress-inducible gene." Thus, the particular control element included in the expression

cassette need not be a stress-inducible control element. Therefore, Applicants are arguing limitations not in the claims. Second, no support is offered for the assertion that the transgenic animals would be characterized by light-generation when administered an analyte, because the expression (or lack thereof) of the reporter gene upon administration of an analyte depends on a number of parameters, including the particular control elements used in the expression cassette, the particular combination of expression cassettes within the mouse, the integration site within the genome, the effect of control elements surrounding the integration site of each cassette, and the particular array of light generating polypeptides used in the various expression constructs introduced into the mouse, all of which are ill-defined by both the specification and the claim limitations.

At page 8 of the response, Applicants argue that the enablement requirement does not require actual working examples. Nevertheless, working examples are one factor that must be considered in the enablement analysis. The MPEP states that "[t]he specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation" (MPEP 2164.02). In this case, it is not. The factors pointing to undue experimentation have been described in detail in the previous Office Actions. Furthermore, it is noted that the court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970). The MPEP states that "[l]ack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art" (MPEP 2164.02).

At page 9 of the response, Applicants assert that Patent Office training materials recognize that claims to transgenic animals are fully enabled where an enabled use for the claimed transgenic mouse is well established. However, in the instant case an enabled use for the claimed transgenic mouse is not well

established. Applicants have pointed to no well established enabled use for the claimed transgenic mouse. Applicants go on to assert that an enabled use for the transgenic animals is well established based on the existence in the prior art of other transgenic animals that express luciferase and the use of those animals for the temporal and spatial analysis of transcriptional control. However, contrary to this assertion the claimed transgenic mouse is quite distinct from the prior art animal and, in the instant case, an **assertion** of utility has been made to use the mice for a distinct purpose which is for identifying the effect of an analyte on gene expression mediated by the control elements present in the expression cassette.

The level of expression of a reporter gene will depend on the particular combination of control elements used to drive and regulate its expression, the "completeness" of the promoter element outside of its native context, and the authenticity of the new context within the genome into which the expression cassette is inserted. The endogenous control elements surrounding the transgene insertion site will affect expression of the reporter cassette, to an unpredictable extent. Preparing a transgene construct necessarily requires the truncation of a gene's upstream promoter elements and subsequent operable linkage of the truncated promoter element to the reporter gene. Ultimately, the expression cassette must be inserted into the mouse genome either randomly or by targeted integration to produce a mouse that expresses the reporter gene in a manner that is representative of and predictive of the activity of the control elements in their native context. The instant specification provides little to no guidance for achieving reporter gene expression that is relevant to native gene expression in a living animal, particularly given the broad scope of the various contol elements covered by the claims and the artificial combinations that are contemplated and covered.

The specification discloses, at pages 11-12, that the "control element derived from a ... stress-inducible gene" may be as follows:

"Typical control elements or expression control elements or regulatory sequences, include, but are not limited to transcription promoters, transcription enhancer elements, transcription termination

signals, polyadenylation sequences (located 3' to the translation stop codon), sequences for optimization of initiation of translation (located 5' to the coding sequence), translation enhancing sequences, and translation termination sequences. Transcription promoters can include inducible promoters (where expression of a polynucleotide sequence operably linked to the promoter is induced by an analyte, cofactor, regulatory protein, etc.), repressible promoters (where expression of a polynucleotide sequence operably linked to the promoter is induced by an analyte, cofactor, regulatory protein, etc.), and constitutive promoters.

Expression enhancing sequences typically refer to control elements that improve transcription or translation of a polynucleotide relative to the expression level in the absence of such control elements (for example, promoters, promoter enhancers, enhancer elements, and translational enhancers (e.g., Shine and Delagarno [sic] sequences))."

Thus, the "control element derived from a ... stress-inducible gene" need not be elements that are in any way themselves inducible. For example, polyadenylation signals are not inducible elements, and therefore, despite the explicit teaching that they would be useful in the claimed invention, in fact logic dictates that they would not. The specification contemplates producing artificial gene regulatory regions by combining control elements from various sources with no guidance on how such constructs would be useful in elucidating the function of control elements in their native context. Thus, it would be up to the skilled artisan to determine, based on extensive experimentation, what guidance in the specification is useful guidance and what is not. Furthermore, in view of the very broad scope of constructs that can be used in the transgenic mice, considerable guidance would be required to correlate the result obtained in the analyte screening assay with the effect of the analyte on native gene expression. However, the specification does not offer such guidance. Thus, the skilled artisan would not be able to obtain a useful result that is relevant to the control element being studied.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 80 is rejected under 35 U.S.C. 102(b) as being anticipated by the JAX Mice Price List (June 1997, page 19).

Claim 80 is directed to an ancestor of the transgenic mouse of claim 38.

The JAX Mice Price List discloses numerous inbred strains of mice. Such mice are sometimes referred to as "wild-type mice" to emphasize that they do not contain artificially introduced genetic modifications. A wild-type mouse is necessarily an ancestor of a transgenic mouse. For example, FVB/NJ mice are often used in the process of making transgenic mice. Claim 38 covers transgenic mice that have both hemizygous and homozygous transgenes. As an example, the parents of a hemizygous transgenic mouse would be a wild-type FVB/NJ mouse crossed to a transgenic founder hemizygous mouse. The wild-type mouse is an ancestor of both the hemizygous and homozygous transgenic mouse.

Thus, the claimed invention is disclosed in the prior art.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER